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RAO, DEEPAK R	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,495	EBDEN ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14 and 17-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060228*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 11-14 and 17-24 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-9, 11-14 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a solvate or in vivo hydrolysable ester of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite "A compound of the formula (I) ... **solvate** or ***in vivo***

hydrolysable ester thereof" wherein there is insufficient description in the specification regarding the types of 'solvates' and '*in vivo* hydrolysable esters' intended by the recitation.

(A) ***In vivo* hydrolysable ester**

The specification at page 5 provides a definition for the term "*in vivo* hydrolysable ester" to represent 'a pharmaceutically acceptable ester which is cleaved in the human body or animal body to produce the parent acid or alcohol'. In the instant case, however, the specification does not provide what are some of the examples of such compounds intended by the term '*in vivo* hydrolysable ester'.

The specification further provides that '*in vivo* hydrolysable esters' include pharmaceutically acceptable esters. There is no disclosure regarding any other compounds of formula (I) having functional groups such as esters, etc. that are capable of providing the corresponding acid compounds of the invention. Since functional groups such as esters, etc. are already included in the claimed compounds, it is not clear whether compounds bearing these groups are excluded from being a potential "*in vivo* hydrolysable ester" of the claimed invention. If compounds bearing these groups (i.e., carboxyl ester, etc.), which are likely to undergo *in vivo* transformation, are excluded then what is included in the definition of the above term and where on the structural formula (I) are these groups placed; the specification does not provide any direction to one of ordinary skill in the art.

a) Finding a prodrug, in this case *in vivo* hydrolysable ester is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug

metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the *in vivo* hydrolysable esters is found in the page 5.

c) There is no working example of a *in vivo* hydrolysable ester of a compound the formula (I).

d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.

e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. A prodrug as defined by Bundgaard (Design of Prodrugs) "is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug" (see page 1). Thus, an important requirement of prodrugs is that they be pharmacologically inactive. The scope of the term '*in*

vivo hydrolysable ester' is quite broad.

f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug". Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

(B) **Solvate**

It is generally known that '**solvate**' is 'a compound formed by combination of solvent molecules with molecules'; the specification, however, has no working examples of "solvate" of a compound of formula (I). Some of the exemplified compounds within the claimed genus were in contact with solvent, yet they have not formed solvate as evident form spectral data provided for these compounds.

Searching the pertinent art in the related pyrimidine area did not result in support for such solvates of instant pyrimidine compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands

factors. Hence, the burden of establishing the *prime facie* case is met with:

(i). **The nature of the invention and the state of the prior art:**

Specification is not adequately enabled as to how to make solvate of compounds of Formula I Specification has no example of solvate of the instant compounds. Specification neither defines the term nor provides an enabling disclosure of 'solvates' of the instant compounds.

The compound of formula I embrace substituted pyrimidine compounds substituted with variable groups X, R^1, R^2, R^3, etc. Careful calculation of the number of compounds embraced in the instant formula I shows a large number of compounds and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different

solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

(ii). **The predictability or lack thereof in the art:**

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

(iii). **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvate of instant compound. Many of the

exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

(iv). **The presence or absence of working examples:**

There is no working example of any solvate formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

(v). **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate of the compound of formula I. As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired **solvate** of compound of formula (I) embraced in the instant claims in view of the pertinent reference teachings.

2. Claims 11-12, 14, 19-21 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of rheumatoid arthritis and osteoarthritis, does not reasonably provide enablement for a method a method of treating allergic rhinitis, asthma, COPD, inflammatory bowel disease, etc.; or a method of treating cancer; or a method of treating a disease or condition in which modulation of chemokine receptor activity is beneficial; or a method of combination therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Claim 14 recites "a method of treating a disease or condition in which **modulation** of chemokine receptor activity is beneficial" and it is generally known that the term "Modulation"

encompasses antagonism, partial antagonism and partial agonism. However, the compounds were not shown to have all these properties. The specification only provides test data related to measuring antagonism of CXCR2 and there is no disclosure, how one of ordinary skill in the art can extrapolate this data to find the 'chemokine modulation' activity of the compounds. For example, it is revolutionary for a compound to be effective as an antagonist and partial agonist/antagonist. The specification did not provide any competent tests or data to establish that the compounds have the claimed 'chemokine receptor modulating activity'. Havlioglu et al. (Journal of Neurovirology 2002) provide that "Chemokines are classified into several families according to their structural features" (page 486); "Although some viral-derived chemokine inhibitors have been reported, very little is known about endogenously produced chemokine inhibitors" (page 487); and conclude that "The studies on the interplay between chemokine pathways and other signal transduction pathways are only at the beginning. Mechanisms underlying the complex regulation of chemokine signaling inside and outside the nervous system await further investigation with combined molecular, biochemical and functional approaches" (page 489). This establishes the uncertainties and the level of unpredictability in the relevant state of the art and therefore, one of ordinary skill in the art would be required to go through undue experimentation to find the modulating activity of the compounds.

The instant claims recites method of treatment of various disorders and the specification fails to enable one skilled in the art for the recited use. The use disclosed in the specification is as therapeutic agents for the treatment of diseases listed in pages 19-21, which includes various inflammatory diseases, etc. First, the claims cover 'disorders' having diverse mechanisms and/or involving various organs and parts of a human body and therefore, the treatment recited in the

claims is extremely broad. Further, there is no description regarding how to identify the subject 'in need of such treatment' of these assorted diseases. Test procedures for measuring the activity of the compounds in terms of antagonism of CXCR2 is provided on pages 29-30, however, there is nothing in the disclosure regarding how this *in vitro* assay correlates to the treatment of the disorders of the instant claims. The data provided in insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of the treatment is identified and further, how all types of disorders of the claims having diverse etiologies are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to all types of disorders of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Enablement for the scope of "treatment of inflammatory disorders" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical

pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name, given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the

eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammatory disorders. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

The therapeutic method of the instant claims includes treatment of inflammatory bowel disease, e.g., Crohn's disease, ulcerative colitis, psoriasis, etc. which have been proven very difficult to treat because 'there is no known cause' (see for example, the online edition of The Merck Manual). Bremner et al. (Expert Opin. Pharmacother. 2002) provide that "New therapies that affect immunomodulation offer the possibility of disease control in those unresponsive to conventional therapy and may reduce the need for further surgery. However, these treatments remain to be fully evaluated" (see page 820). Singh et al. (British Journal of Surgery, 2001) provide that 'the etiology and pathogenesis of inflammatory bowel diseases are incompletely understood' (see page 1558). Robinson (Eur. J. Surg. 1998) indicates that "Despite the growing list of medications and formulations prompted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective"; "All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders" (see page 90). This state of the art analysis indicative of the unpredictability related to the treatment of inflammatory bowel diseases.

The instant claims include 'a method of treating cancer' and the terms 'cancer' and 'proliferative disorders' represent anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. The state of the art is not indicative any pharmaceutical agents that are useful in the treatment of cancer generally. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or preventing' effect of a 'disease' solely based on the *in vitro* MCP-1 antagonizing activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating a disease or condition in which modulation of chemoline receptor activity is beneficial, which includes diseases such as inflammatory diseases, cancer, etc.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat all types of diseases embraced by the instant claims.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders cited, etc. nor there are doses given for the treatment of the disorders recited. The specification provides test procedures (see pages 29-30) to test the compounds *in vitro* and indicates that the compounds of the invention have activity in the antagonism of CXCR2. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests.

6) The breadth of the claims: The instant claims embrace treating all diseases associated with modulation of chemokine receptor activity, etc., which diseases include inflammatory diseases, cancer, etc.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11-14 and 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Recitation of "*in vivo* hydrolysable ester" through out the claims renders these claims and their dependent claims indefinite. The term is explained to represent 'pharmaceutically acceptable esters' (as per specification page 5), which undergo *in vivo* hydrolysis. In that sense recitation of "*in vivo* hydrolysable esters" is not ambiguous and is acceptable. However, the definition of various substituents groups on pyrimidine include such groups, namely esters, etc., see e.g., the definition of R^2 wherein the carbocyclyl is substituted with $-COOR^7$ wherein R^7 is hydrogen, alkyl or phenyl. Therefore, the instantly claimed formula (I) already includes esters, which are *in vivo* hydrolysable and also, the corresponding acids. Therefore it is not clear what is the difference between

these variable groups and the "*in vivo* hydrolysable ester" groups. The use of ester group(s), etc. as substituents as well as in '*in vivo* hydrolysable ester' as Markush choice, results in ambiguity.

2. Claim 18 recites the limitation "converting the compound of formula (1) into a further compound of formula (1), ... iv) **forming a prodrug**" in all the steps (a) to (d), see e.g., lines 7-10 of the claim. There is insufficient antecedent basis for this limitation in claim 1 on which claim 18 is dependent. Claim 1 does not recite 'a prodrug' of the compound of formula (1).
3. Claim 19 is drawn to 'a method of combination therapy', however, the claim does not set forth the precise metes and bounds of the claim. The claim does not properly recite the type of 'patient or subject' to which the combination therapy is provided. It is not clear what is intended by the term "other therapy" in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-2, 4-5, 8, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Minami et al., U.S. Patent No. 3,673,184 (cited in IDS). The instant claims read on reference disclosed compound, see the compound 4 in Table II.

2. Claims 1-2, 4-6, 8, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Nogimori et al. (cited in IDS). The instant claims read on reference disclosed compound, see the compounds (8) and (9) in page 1694.
3. Claims 1-2, 4-5, 8, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 61-118372 (cited in IDS) or the corresponding CAPLUS Abstract 106:18604 (1987). The instant claims read on reference disclosed compound, see the compound the reference.
4. Claims 1-8, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Huebsch et al. (cited in IDS). The instant claims read on reference disclosed compound, see the compounds 5, 6, 25, 26 in page 1380.
5. Claims 1-8, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 31-197467 (cited in IDS) or the corresponding CAPLUS Abstract 115:280054 (1991). The instant claims read on reference disclosed compound, see the compound the reference.
6. Claims 1-2, 4-6, 8, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cobo et al. (cited in IDS). The instant claims read on reference disclosed compound, see the compound 10d in page 10348.
7. Claims 1-8 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/76980 (cited in IDS). The instant claims read on reference disclosed compound, see the compounds 8-1 to 8-20 in Table 3 (pages 32-33).

Receipt is acknowledged of the Information Disclosure Statement filed on February 28, 2006 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

September 25, 2007